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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER

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ART UNIT

PAPER NUMBER

1632
DATE MAILED:

02/14/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/358,937

Applicant(s)

SPRADLING ET AL.

Examiner

Joseph T. Voitach

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 November 2000.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-36 is/are pending in the application.
- 4a) Of the above claim(s) 3, 11-15, 17, 19-22, 32 and 34 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 2, 4-10, 16, 18, 23-31, 33, 35, and 36 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- 15) ☒ Notice of References Cited (PTO-892)
- 16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7, 8.
- 18) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 19) ☐ Notice of Informal Patent Application (PTO-152)
- 20) ☐ Other: _____

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DETAILED ACTION

Please note that the Examiner of record and art unit has changed. The Examiner of record is now **Joseph T. Woitach** and the group art unit is now **1632**.

This application is an original application filed July 23, 1999 which claims benefit to provisional application 60/094,008, filed July 24, 1998.

Election/Restriction

Applicants response to the restriction requirement filed November 21, 2000 (paper number 11) has been received and entered. Applicant's election with traverse of Group I in Paper No. 11 is acknowledged. Further, Applicants elect species 3(b) *in vivo* methods and species 4(c)(i) transduction with nucleic acid and further Dpp, and state that claims 1-18, 23, 24, 28-31, 33, 35 and 36 read on the elected species. The traversal is on the ground(s) that Group II should be examined with Group I since all the limitations of claim 1 are incorporated into Group II and would not require an undue burden to examine. Further, Applicants argue that examination of claim 25 would necessarily require the examination of claim 1. In addition, Applicants request a clarification of the division of species in paragraph 4 since they do not seem mutually exclusive. Applicants arguments have been fully considered.

Examiner agrees in part with Applicants arguments. Though Group II represents a patentable distinct invention, Examiner agrees it would not be an undue burden to exam claims

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25-27 with elected claims of Group I and will be reviewed to the extent that they encompass the elected invention. With respect to paragraph 4, each species represent a patentably distinct species that would not anticipate the other. The materials and method steps used in each of the species is different and unique to each species. For example, the use of feeder cells or administration of a protein to a culture does not require any further modification of the germline stem cell, however these differ as starting material and specific methods steps needed to practice the use of each species. These two species differ from the remaining three because the germline cell must be genetically modified to practice the three remaining methods. Each of the three remaining methods differ one from the other because of the type of genetic alteration, consequence and material needed to affect the changes are different. The species of 4c are secreted proteins which activate a cell surface receptor, 4d represents the receptors themselves, and 4e represents signaling molecules downstream of the receptor. Creating the genetic alteration and methods of using each of the specific genetic changes (such as level of expression, culturing conditions) encompasses materials and methods which would not anticipate the other remaining species. In addition, claims 11-15, 17 are withdrawn from consideration because they encompass genetically altering genes other than Dpp.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-36 are pending. Claims 3, 11-15, 17, 19-22, 32, 34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election)

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requirement in Paper No. 11. Claims 1, 2, 4-10, 16, 18, 23-31, 33, 35 and 36 are currently under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 4-10, 16, 18, 23-31, 33, 35 and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claim 1 is vague and unclear in the recitation 'stimulating signal transduction by a bone morphogenetic protein (BMP) signaling pathway in at least one cell of said population' because of the open language of a population of cells, it is unclear if the method is directed to stimulating the pathway in the germline stem cell directly or in another cell in the population which in turn results in the maintenance of the germline stem cells. Further the preamble recites a method for maintaining germline stem cells, however practice of the claimed method results in an increase number of cells.

Claim 2 is unclear in the recitation of 'said Drosophila' because there is no antecedent basis for a Drosophila in claim 1 only cells from a Drosophila.

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Claim 7 is vague, unclear and indefinite in the recitation of 'stimulated by providing at least 10% more Decapentaplegic (Dpp) activity' because the type of activity of the Dpp is not defined. It is known in the art that BMP is a large family of molecules which has different effects on different cells, so different activities depend both on the cell affected and the specific BMP used. In addition, there are many forms of Dpp (for example, dpp^{c90} , dpp^{hr4} , dpp^{hr56} specification, Table 1 and art (rd) and it is unclear if recitation of 'Dpp' encompass these alternative forms of the wild type Dpp or only the wild type Dpp. Further, it is unclear what is meant by 'stimulated' because it is not clear what is encompassed by the BMP signaling pathway, therefore what is encompassed as being stimulated is unclear and indefinite.

Claims 9, 16, 35 and 36 are unclear in the recitation of 'stimulated/stimulating' because it is not clear what is encompassed by the BMP signaling pathway, therefore what is encompassed as being stimulated is indefinite.

Claim 10 recites a Dpp protein, BMP-2 and BMP-4, however the elected invention is drawn to the delivery of a nucleic acid encoding Dpp.

Claim 26 is unclear and confusing because the method of claim 1 is for the maintenance of germline stem cells however claim 26 encompasses differentiation of the cell and not maintenance. It is unclear how one can practice the method of claim 1 for maintaining germline stem cells and simultaneously also differentiate them into other lineages.

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Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4-10, 16, 18, 23, 24, 28-31, 33, 35 and 36 are rejected under 35

U.S.C. 102(b) as being anticipated by Twombly *et al.*

Claims 1, 2, 4-10, 16, 18, 33, 35 and 36 encompass a method of maintaining germline stem cells of *Drosophila* comprising providing a population of germline cells and stimulating transduction by BMP, specifically by expressing a transgene which encodes Dpp. Claims 23 and 24 require that the germline stem cells maintained are totipotent and pluripotent. Claims 28-31 encompass mutating or introducing a second gene into the cells genome. Twombly *et al.* teach a transgenic *Drosophila* wherein the transgene expressed is Dpp (page 1556; second column). The transgenic *Drosophila* contains all cells normally found in *Drosophila* including germline stem cells. Twombly *et al.* summarize previous experiments stating that dpp is not required during oogenesis (Irish and Gilbert) however, that it's signal and signal pathway is required by the germline stem cells (page 1556; middle of first column). Further, Twombly *et al.* teach that there is a 150% increase in the size of the opercula indicating an increase in Dpp activity due to transgene expression. Though Twombly *et al.* do not specifically examine the pluripotent or

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totipotent state of the germline stem cells, the method practiced by Twombly *et al.* would inherently result in the increased maintenance of the germline stem cells. Finally, Twombly *et al.* teach the expression and disruption of the sax gene as well as the use of FLP and various alternate forms of dpp (page 1556; materials and methods section). Thus, the claimed invention is anticipated.

Claims 1, 2, 4-10, 16, 18, 23, 24, 28-31, 33, 35 and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by Forbes *et al.*

Claims 1, 2, 4-10, 16, 18, 23, 24, 28-31, 33, 35 and 36 are summarized above. Forbes *et al.* teach the ectopic expression of Dpp in *Drosophila* through the expression of a transgene (entire reference, in particular material and methods section). Forbes *et al.* specifically observe that expression of Dpp results in a multiplicity of germline cells in the ovary (page 3291; first and second column bridging paragraph and figure 7). Further, Forbes *et al.* teach the expression of several other transgenes such as hh, en, and wg (page 3284; material and methods), and the ptc gene is disrupted resulting in the lack of activity of said gene (page 3285; bottom of first column). Thus, Forbes *et al.* anticipate the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 25-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Forbes *et al.* or Twombly *et al.* and Lin *et al.*

Claim 1 is summarized above. Claims 25-27 encompass a method further comprising transferring the stimulated germline stem cells into a host *Drosophila*. Forbes *et al.* or Twombly *et al.* each teach a method wherein Dpp is expressed as a transgene in *Drosophila* resulting either inherently or as observed by Forbes *et al.* in the increase in germline stem cells. Further, each reference teach the additional expression and disruption of genes in the *Drosophila* genome. However, neither reference teaches the transfer of germline stem cells into a host *Drosophila*. Lin *et al.* teach the transfer of germline stem cells into a host *Drosophila* for the study of germarial cells (entire reference; summarized in the abstract). Thus, it would have been *prima facie* obvious for one of ordinary skill in the art at the time of the claimed invention to use the methods of germarial cell transfer as taught by Lin *et al.* to implant the stimulated germline stem cells as taught by Forbes *et al.* and Twombly *et al.* One would have been motivated to transfer these cells to examine the influence of transgene behavior on oogenesis or other parts of development as Lin *et al.* did for various strains/genotypes of donor and host *Drosophila*. There would have been an reasonable expectation of success given the results of Lin *et al.* with the multiple different

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strains of *Drosophila* to transfer stimulated germline stem cells as taught in Forbes *et al.* and Twombly *et al.* for the further study of germlial development.

Thus, the claimed invention is *prima facie* obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach, whose telephone number is (703) 305-3732. The examiner can normally be reached on Monday through Friday from 8:00 to 4:30 (Eastern time).

If attempts to reach the examine by telephone are unsuccessful, the examiner's supervisor, Karen M. Hauda, can be reached on (703) 305-6608. The fax number for group 1600 is (703)308-4724.

An inquiry of a general nature or relating to the status of the application should be directed to Kay Pickney whose telephone number is (703) 305-3553.

Joseph T. Woitach

Woitach
JALD:MAF
PATENT EXAMINER
11/16/32